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10/618,934	07/14/2003	Laurens Nicolaas Sierkstra	4322.230-US	6607
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			EXAMINER MOORE, WILLIAM W	
			ART UNIT 1656	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

## Office Action Summary

**Application No.**

10/618,934

**Applicant(s)**

SIERKSTRA ET AL.

**Examiner**

William W. Moore

**Art Unit**

1656

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 06 November 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 88-96 and 99-117 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 88-96 and 99-117 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## DETAILED ACTION

*Response to Amendment*

Applicant's amendments filed 11 November 2007 overcome the objections of record of claims 96, 102, and 106 herein, as well as the rejections of record of claims herein under 35 U.S.C. § 102. The claim amendments permit the withdrawal of the obviousness-type double patenting [ODP] rejections of the claims pending herein over the claims of US Patent 5,631,217 and the claims of the co-pending application serial No. 10/699,394. The claim amendments necessitate further grounds of rejection, however, under 35 U.S.C. §§ 102(e) and 103(a).

The obviousness-type double patenting rejection of record of claims herein over the claims of US Patent No. 6,777,218, severally owned both by Applicant and a co-assignee other than the co-assignee of the instant application is also withdrawn because the cited patent is severally assigned to the present Applicant and an assignee other than the two assignees of the instant application and a Terminal Disclaimer cannot properly be required to prevent an unjustified, or improper timewise extension of the "right to exclude" granted by that patent, or the possible harassment by multiple assignees, where the rights conferred are shared by another and the assignees are already multiple but are not congruent with those of the instant application.

*Response to Request for Withdrawal of Terminal Disclaimer*

Applicant requests at page 7 of the Response filed 6 November 2007 that the Terminal Disclaimer filed 18 December 2006 be withdrawn at page 7 of the Response filed 11 November 2007, arguing that, while it is commonly-assigned, the instant application is not wholly owned by Applicant, and that the three patents cited in the Terminal Disclaimer, while all are commonly-assigned, are also not wholly owned by Applicant, and the Terminal Disclaimer was required unnecessarily. Applicant's argument is not persuasive. The assignees of the three terminally disclaimed patents are the same assignees of the instant, successor, application, thus the rights conferred by these three patents are clearly commonly-assigned, i.e., no further assignee is implicated, and withdrawing the terminal disclaimer would grievously violate the public policy of preventing the unjustified or improper timewise extension of the "right to exclude" granted by patented claims over which claims pending herein remain patentably indistinct. The Terminal Disclaimer filed 18 December 2006 was properly required and may not be withdrawn.

*Double Patenting: Non-Statutory*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29

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USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

At pages 7-9 of the Response filed 6 November 2007 Applicant presents an argument corollary to the request for withdrawal of the previously-filed Terminal Disclaimer, suggesting that the ODP rejections of record herein were improper and unnecessary where (i) the instant application has a further assignee, thus is severally owned, (ii) all but one of the US patents and co-pending applications cited in the rejections of record are instead wholly-owned by Applicant, and (iii) US Patent No. 6,777,218 is severally owned by Applicant and a co-assignee other than the co-assignee of the instant application. The ODP rejection of the latter is withdrawn above. Applicant does not argue that the ODP rejections of record should be withdrawn because there is no need to prevent harassment by multiple assignees, indeed there is no evidence that the co-assignees of the instant application disagree with the prosecution thereof. Neither does Applicant argue that withdrawing the rejections of record would not affect the public policy of preventing unjustified or improper timewise extension of the "right to exclude" granted by patented claims that remain patentably indistinct from claims pending herein.

Where there is no evidence in the record that the co-assignee of the instant application opposes its prosecution, overcoming the rejections of record that cite Applicant's wholly-owned US patents and co-pending applications by filing a terminal disclaimer would clearly prevent the unjustified or improper timewise extension of the "right to exclude" already granted by patented claims, and currently sought in claims of a copending application, over which the claims pending herein remain patentably indistinct, in accord with the public policy enunciated in the appellate decisions cited above. Whether or not the absence of a terminal disclaimer might permit the co-assignee of the instant application to improperly enjoy an unjustified or improper extension of the "right to exclude", the lack of a terminal disclaimer by Applicant would permit Applicant to improperly enjoy an unjustified or improper extension of the "right to exclude" others from practicing previously patented subject matter. The requirement for a terminal disclaimer is also considered to prevent harassment of the assignees of a patent issuing on the instant application because Applicant is the sole assignee of the US patents and co-pending applications cited in the rejections of record, where only terminally-disclaimed rights could be conveyed and these

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patents and copending applications are not shared. Maintaining the rejections of record of claims herein over claims of the patents and the copending applications wholly owned by the Applicant which is the co-assignee prosecuting the instant application will thus sustain the public policies enunciated in the appellate decisions cited above.

1. Claims 88, 92, and 95 remain rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 34, 56, 90, 111, and 121-123 of US Patent 5,741,694. Although the conflicting claims are not identical, they are not patentably distinct from each other because modified subtilases, and compositions comprising same, of claims 88, 92, and 95 comprise amino acid substitutions at the subtilisin BPN'-correspondent position 194 and the patented claims describe modified subtilases, and compositions comprising same, having generic substitutions at this position, particularly where a generic substituent of the patented claims is disclosed to be among a limited number of naturally-occurring amino acids each of which would be obvious to the artisan and where no particular property is conferred on a modified subtilase by any substituent recited in claims 88 and 92 herein.

2. Claims 88-90 and 92-95 are now rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 4, 7, and 9-14 of U.S. Patent No. 6,555,355. Although the conflicting claims are not identical, they are not patentably distinct from each other because modified subtilases, and compositions comprising same, of claims 88-90 and 92-95 comprise amino acid substitutions at the subtilisin BPN'-correspondent positions 167, 170, and 194 as well as at least one ancillary substitution or deletion at one or more of the positions 36, 57, 76, 97, 104, 120, 206, 218, 222, and 235, and because the patented claims describe modified subtilases, and compositions comprising same, having generic substitutions at these positions, particularly where generic substituents of the patented claims are disclosed to be among a limited number of naturally-occurring amino acids each of which would be obvious to the artisan and where no particular property is conferred on a modified subtilase by any substituent recited in claims 88-90 and 92-95 herein.

3. Claims 88-90 and 92-95 are now rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-14 of U.S. Patent No. 6,558,938. Although the conflicting claims are not identical, they are not patentably distinct from each other because modified subtilases, and compositions comprising same, of claims 88-90 and 92-95 comprise amino acid substitutions at the subtilisin BPN'-correspondent positions 167, 170, and 194 as well as at least one ancillary substitution or deletion at one or more of the positions 36, 57, 76, 97, 104, 120, 206, 218, 222, and 235, and because the patented claims

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describe modified subtilases, and compositions comprising same, having generic substitutions at these positions, particularly where generic substituents of the patented claims are disclosed to be among a limited number of naturally-occurring amino acids each of which would be obvious to the artisan and where no particular property is conferred on a modified subtilase by any substituent recited in claims 88-90 and 92-95 herein.

4. Claims 88-90 and 92-95 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-19, 23, 38-41, 45, 65-68 and 72 of US Patent 6,605,458. Although the conflicting claims are not identical, they are not patentably distinct from each other because subtilases, and compositions comprising same, of claims 88-90 and 92-94 have an amino acid substitution at any of the subtilisin BPN'-correspondent positions 167, 170 and 194 and the patented claims describe modified subtilases, and compositions comprising same, having generic substitutions at any these positions that may further comprise at least another substitution or deletion at one or more of positions 36, 57, 76, 97, 104, 120, 206, 218, 222, and 235, particularly where a generic substituent of the patented claims is disclosed to be among a limited number of naturally-occurring amino acids each of which would be obvious to the artisan and where no particular property is conferred on a modified subtilase by any substituent recited in claims 88-90 and 92-94 herein.

5. Claims 88-90 and 92-95 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 10-12, 14, 20, 35-37, 39, 45, 60-62, 64, 70, 86-88, 90, 96, 111-113, 115, 121, 136-138, 140, 146, 161-163, 165, 171, 186-188, 190, 196, 211-213, 215, and 221 of US Patent 6,773,907. Although the conflicting claims are not identical, they are not patentably distinct from each other because modified subtilases, and compositions comprising same, of claims 88-90 and 92-95 have an amino acid substitution at any of the subtilisin BPN'-correspondent positions 167, 170, and 194 and the patented claims describe modified subtilases, and compositions comprising same, having generic substitutions at any of these positions that may further comprise at least one ancillary substitution or deletion at any of positions 36, 57, 76, 97, 104, 120, 194, 206, 218, 222, and 235, particularly where a generic substituent of the patented claims is disclosed to be among a limited number of naturally-occurring amino acids each of which would be obvious to the artisan and where no particular property is conferred on a modified subtilase by any substituent recited in claims 88-90 and 92 herein.

6. Claims 88-90 and 92-95 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-11, 13, 19, 33-35, 37,

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43, 57-59, 61, 67, 81-83, 85, 91, 105-107, 109, 115, 129-131, 133, 139, 153-155, 157, 163, 177-179, 181, and 187 of US Patent 6,780,629. Although the conflicting claims are not identical, they are not patentably distinct from each other because modified subtilases, and compositions comprising same, of claims 88-90 and 92-95 have an amino acid substitution at any of the subtilisin BPN'-correspondent positions 167, 170, and 194 and the patented claims describe modified subtilases, and compositions comprising same, having generic substitutions at any these positions that may further comprise at least another substitution or deletion at one or more of positions 36, 57, 76, 97, 104, 120, 194, 206, 218, 222, and 235, particularly where a generic substituent of the patented claims is disclosed to be among a limited number of naturally-occurring amino acids each of which would be obvious to the artisan and where no particular property is conferred on a modified subtilase by any substituent recited in claims 88-90 and 92 herein.

7. Claims 88, 90, and 92-95 remain rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6 and 7 of US Patent 6,808,913. Although the conflicting claims are not identical, they are not patentably distinct from each other because modified subtilases, and compositions comprising same, of claims 88, 90, and 92-95 have an amino acid substitution at either of the subtilisin BPN'-correspondent positions 170 and 194 and the patented claims describe modified subtilases, and compositions comprising same, having generic substitutions at either of these positions that may further comprise at least another substitution at either of positions 222 or 235, particularly where a generic substituent of the patented claims is disclosed to be among a limited number of naturally-occurring amino acids each of which would be obvious to the artisan and where no particular property is conferred on a modified subtilase by any substituent recited in claims 88, 90, and 92 herein.

8. Claims 88-90 and 92-95 remain rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-22, 25, and 26 of US Patent 6,893,855. Although the conflicting claims are not identical, they are not patentably distinct from each other because modified subtilases, and compositions comprising same, of claims 88-90 and 92-95 have an amino acid substitution at any of the subtilisin BPN'-correspondent positions 167, 170 and 194 and the patented claims describe modified subtilases, and compositions comprising same, having generic substitutions at any of these positions that may further comprise at least another substitution or deletion at one or more of positions 36, 57, 76, 97, 104, 120, 194, 206, 218, 222, and 235, particularly where a generic substituent of the patented claims is disclosed to be among a limited number of naturally-

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occurring amino acids each of which would be obvious to the artisan and where no particular property is conferred on a modified subtilase by any substituent recited in claims 88-90 and 92 herein.

9. Claims 88-90 and 92-95 remain rejected for reasons of record, under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5, 8, 14, 18, 21, and 27 of US Patent 6,921,657. Although the conflicting claims are not identical, they are not patentably distinct from each other because modified subtilases, and compositions comprising same, of claims 88-90 and 92-95 have an amino acid substitution at any of the subtilisin BPN'-correspondent positions 167, 170, and 194 and the patented claims describe modified subtilases, and compositions comprising same, having generic substitutions at any of these positions that may further comprise at least another substitution or deletion at one or more of positions 36, 57, 76, 97, 104, 120, 194, 206, 218, 222, and 235, particularly where a generic substituent of the patented claims is disclosed to be among a limited number of naturally-occurring amino acids each of which would be obvious to the artisan and where no particular property is conferred on a modified subtilase by any substituent recited in claims 88-90 and 92 herein.

10. Claims 88-90 and 92-95 remain rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14 and 19 of US Patent 7,026,153. Although the conflicting claims are not identical, they are not patentably distinct from each other because modified subtilases, and compositions comprising same, of claims 88-90 and 92-95 have an amino acid substitution at any of the subtilisin BPN'-correspondent positions 167, 170, and 194 and patented claims describe modified subtilases, and compositions comprising same, having generic substitutions at any of these positions that may further comprise at least another substitution or deletion at one or more of positions 36, 57, 76, 97, 104, 120, 194, 206, 218, 222, and 235, particularly where a generic substituent of the patented claims is disclosed to be among a limited number of naturally-occurring amino acids each of which would be obvious to the artisan and where no particular property is conferred on a modified subtilase by any substituent recited in claims 88-90 and 92 herein.

11. Claims 88-91 and 93-95 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4, 5, 7, 8, and 16 of US 7,098,017. Although the conflicting claims are not identical, they are not patentably distinct from each other because modified subtilases, and compositions comprising same, of claims 88-91 and 93-95 have an amino acid substitution at any of the subtilisin BPN'-correspondent positions 167, 170, and 171 and the patented claims describe modified subtilases, and compositions



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comprising same, having generic substitutions at any of these positions that may further comprise at least another substitution or deletion at one or more of positions 27, 36, 57, 76, 97, 101, 104, 120, 123, 206, 218, 222, 224, 235, and 274, particularly where a generic substituent of the patented claims is disclosed to be among a limited number of naturally-occurring amino acids each of which would be obvious to the artisan and where no particular property is conferred on a modified subtilase by any substituent recited in claims 88-91 herein.

12. Claims 88-90 and 92-95 remain rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11 and 26 of US Patent 7,109,016. Although the conflicting claims are not identical, they are not patentably distinct from each other because modified subtilases, and compositions comprising same, of claims 88-90 and 92-95 have an amino acid substitution at any of the subtilisin BPN'-correspondent positions 167, 170, and 194 and the patented claims describe modified subtilases, and compositions comprising same, having generic substitutions at any of these positions, and compositions comprising same, that may further comprise at least another substitution or deletion at one or more of positions 36, 57, 76, 97, 104, 120, 206, 218, 222, and 235, particularly where a generic substituent of the patented claims is disclosed to be among a limited number of naturally-occurring amino acids each of which would be obvious to the artisan and where no particular property is conferred on a modified subtilase by any substituent recited in claims 88-90 and 92 herein.

13. Claims 88-90 and 92-95 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 25 and 27 of US Patent No. 7,192,757. Although the conflicting claims are not identical, they are not patentably distinct from each other because modified subtilases, and compositions comprising same, of claims 88-90 and 92-95 have an amino acid substitution at any of the subtilisin BPN'-correspondent positions 167, 170, and 194 and the patented claims describe modified subtilases, and compositions comprising same, having generic substitutions at any of these positions that may further comprise at least another substitution or deletion at one or more of positions 27, 36, 76, 97, 101, 104, 120, 123, 206, 218, 222, and 235, particularly where a generic substituent of the patented claims is disclosed to be among a limited number of naturally-occurring amino acids each of which would be obvious to the artisan and where no particular property is conferred on a modified subtilase by any substituent recited in claims 88-90 and 92 herein.

The following rejection is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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Claims 88, 90, and 93-95 remain provisionally rejected for reasons of record under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 25, 28, 29, and 32-34 of the copending application serial No. 10/896,177. Although the conflicting claims are not identical, they are not patentably distinct from each other because modified subtilases, and compositions comprising same, of claims 88, 90, and 93-95 herein have an amino acid substitution at the subtilisin BPN'-correspondent position 170 and the cited claims of application 10/896,177 describe modified subtilases, and compositions comprising same, having generic substitutions at any of these positions that may further comprise at least another substitution or deletion at one or more of positions 36, 218, and 222, particularly where generic substituents of the copending claims are disclosed to be among a limited number of naturally-occurring amino acids each of which would be obvious to the artisan and claims 88 and 90 herein require no particular property for a subtilase modified by any recited substituent.

*Claim Rejections - 35 USC §§ 102 and 103*

The following is a quotation of the appropriate paragraphs of 35 USC § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a)(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 USC § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 88, 89, and 93-95 are rejected under 35 USC § 102(e) as being anticipated by any of Brode et al. US 6,436,690, Brode et al. US 6,599,730, or Brode et al. US 6,455,295, all made of record herewith.

This new ground of rejection is necessitated by Applicant's amendment that deletes "Trp" from claims 88 and 89. Brode et al. '690 disclose the preparation of variant subtilisins BPN' wherein (i) methionine or proline are advantageously substituted for the amino acid at position 167, (ii) asparagine is advantageously substituted for the amino acid at position 97, (iii) alanine or asparagine are advantageously substituted for the amino acid at position 104, (iv) glutamate

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is advantageously substituted for the amino acid at position 206, (v) serine is advantageously substituted for the amino acid at position 218, and (vi) that any of these may be advantageously combined with other substitutions in subtilisin BPN'. Brode et al. '690 also disclose that variant subtilisins BPN' may be comprised in detergent compositions for cleaning textiles or hard surfaces. See cols. 4-7 and 51-63.

Similarly, Brode et al. '730 disclose the preparation of variant subtilisins 309 wherein (i) methionine or proline are advantageously substituted for the tyrosine at position 161 in subtilisin 309, corresponding to position 167 in subtilisin BPN', (ii) asparagine is advantageously substituted for the amino acid at position 95 in subtilisin 309, corresponding to position 97 in subtilisin BPN', (iii) alanine or asparagine are advantageously substituted for the amino acid at position 102 in subtilisin 309, corresponding to position 104 in subtilisin BPN', (iv) glutamate is advantageously substituted for the amino acid at position 200 in subtilisin 309, corresponding to position 206 in subtilisin BPN', (v) serine is advantageously substituted for the amino acid at position 212 in subtilisin 309, corresponding to position 218 in subtilisin BPN', (vi) that aspartate may be substituted for the amino acid at position 74 in subtilisin 309, corresponding to position 76 in subtilisin BPN', and (vii) that any of these may be advantageously combined other substitutions in subtilisin 309. Brode et al. '740 also disclose that the variant subtilisins 309 may be comprised in detergent compositions for cleaning textiles. See cols. 5-12 and 96-109.

Brode et al. '295 likewise disclose the preparation of variant subtilisins Carlsberg wherein (i) methionine or proline are advantageously substituted for the amino acid at position 166 in subtilisin Carlsberg, corresponding to position 167 in subtilisin BPN', (ii) asparagine may advantageously be substituted for the amino acid at position 96 in subtilisin Carlsberg, corresponding to position 97 in subtilisin BPN', (iii) alanine or asparagine are advantageously substituted for the amino acid at position 103 in subtilisin Carlsberg, corresponding to position 104 in subtilisin BPN', (iv) glutamate is advantageously substituted for the amino acid at position 205 in subtilisin Carlsberg, corresponding to position 206 in subtilisin BPN', (v) serine may be substituted for the amino acid at position 217 in subtilisin Carlsberg, corresponding to position 218 in subtilisin BPN', (vi) and that any of these substitutions may be advantageously combined with another of these substitutions in subtilisin Carlsberg. Brode et al. '740 also disclose that variant subtilisins Carlsberg are advantageously comprised in detergent compositions suitable for cleaning textiles. See cols. 4-7 and 83-96.

Claims 88, 90, and 93-95 are rejected under 35 USC § 102(e) as being anticipated by Mulleners et al. US 6,287,841.

This new ground of rejection is not necessitated by any amendment of Applicant, thus this communication is not made final. Mulleners et al. '841, cited and discussed at page 10 of the communication mailed 9 May 2007, teach the preparation of variant subtilisins 309 and PB92 comprising substitutions of isoleucine, valine, and methionine for the amino acid at position 164, corresponding to position 170 in subtilisin BPN', meeting limitations of claims 88 and 90. See col. 5 and cols. 11 & 12, Tables II and III. Mulleners et al. '841 also disclose that variant subtilisins 309 and PB92 may be comprised in detergent compositions. See. e.g., claim 22.

Claims 88 and 92 are rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Christianson et al., US 5,340,735.

This new ground of rejection was not required by any amendment of Applicant, thus this communication is not made final. Christianson et al. '690, cited and discussed at page 17 of the communication mailed 25 August 2005, disclose the preparation of variant subtilisins of a strain of *Bacillus lentus*, designated DSM5483, wherein the amino acid at position 188, corresponding to position 194 in subtilisin BPN', is advantageously substituted by any "small hydrophobic amino acid[ ]" listed at col. 8, lines 51-52, including isoleucine and valine, meeting limitations of claim 88. See col. 9 at line 11.

In the alternative, it would have been obvious to one of ordinary skill in the art at the time the invention was made to regard Christianson et al. as teaching the advantage of substituting valine or isoleucine for an amino acid present at the subtilisin BPN'-correspondent position 194 in any *Bacillus lentus* subtilisin in view of the further teaching of Christianson et al. that such substitutions increase internal van der Waals interactions, thus render the variant subtilisin more stable than an unmodified subtilisin, providing such an artisan with ample motivation to do so.

Claims 96 and 99-109 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rasmussen et al. US 6,110,884, and Mulleners et al., US 6,287,841, in view of Branner et al., US 5,482,849, and Brode et al. US 6,599,730, all of record.

Rasmussen et al., cited and discussed at page 18 of the communication mailed 16 June 2006, teach the preparation of variant subtilisins 309 and 147 comprising Y171I, Y171L, Y171S, Y171Q, Y171N, and Y171H substitutions at the subtilisin BPN'-correspondent position 171 as well as detergent compositions comprising same. See claims 1-3 and 8. Rasmussen et al. also teach that variant subtilisins 309 and 147 may further comprise any of amino acid substitutions of S99G, S101G, V104A, V104N, V104Y, and M222S, numbered by correspondence with the amino acid sequence of subtilisin BPN'. See col. 5, line 33, through col. 6, line 6, and claims 3, 9-15, and 22. Mulleners et al. teach preparation of variant subtilisins 309 and PB92 comprising multiple amino acid substitutions, including a cysteine substitution for the amino acid at position 134 in subtilisins 309 and PB92, corresponding to position 136 in subtilisin BPN', as well as

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detergent compositions comprising such variant subtilisins. See col. 5, line 60, col. 8, lines 20-28, and claims 16, 17, and 22. Teachings of Brode et al. '730, discussed above, are taken as before of the amino acid substitutions of (i) asparagine at the subtilisin BPN'-correspondent position 97, (ii) alanine or asparagine at the subtilisin BPN'-correspondent position 104, (iii) glutamate at the subtilisin BPN'-correspondent position 206, (iv) serine at the subtilisin BPN'-correspondent position 218, and (v) that any of these are advantageously combined with other substitutions in a variant subtilisin 309. The teachings of Branner et al., discussed at page 11 of the communication mailed 9 May 2007 are also cited, of preparing variant, generic, subtilisins wherein substitutions at the subtilisin BPN'-correspondent position 171 are combined with other substitutions, including K27R, H120D, and K235L, or combined with the amino acid insertion \*36D, where the modified subtilisin e may be any of "subtilisin 309, subtilisin 147 [and] Bacillus PB92 protease" and several other subtilisins. See claims 5 and 20.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the amino acid sequences of the subtilisins 309, 147, and PB92, according to claims 96, 102 and 106 herein by introducing one of the amino acid substitutions Y171I, Y171L, Y171S, Y171Q, Y171N, and Y171H taught by Rasmussen et al. and to combine one of these substitutions with the cysteine substitution at position 136 taught by Mulleners et al. as well as to further combine the pair of substitutions with one or more of the S101G, V104A, V104N, V104Y, and M222S substitutions of Rasmussen et al. and/or one or more of the K27R, H120D, and K235L substitutions and/or \*36D insertion of Branner et al. according to claims 99, 100, 103, 104, 107, and 108 herein, as well as to prepare detergent compositions of claims 101, 105, and 109 herein comprising such multiply-modified subtilisins. This is because (1) Rasmussen et al. and Branner et al. both teach that amino acid substitutions at subtilisin BPN'-correspondent position 171 are advantageously combined with further amino acid modifications, including the K27R, H120D, and K235L substitutions and/or a \*36D insertion in a great variety of subtilisins, (2) Mulleners et al. teach that their substitution may be combined with further amino acid substitutions, and (3) because Rasmussen et al. teach that their amino acid substitutions are also advantageously combined with other substitutions. Such an artisan would have had a reasonable expectation of success in combining any of the substitutions of Rasmussen et al. at the subtilisin BPN'-correspondent position 171 with the substitution of Mulleners et al. at the subtilisin BPN'-correspondent position 136, as well as one or more of the further amino acid sequence modifications of Rasmussen et al. and Branner et al. in any of subtilisins 309, 147, and PB92 where Branner et al. teach that different subtilisins are amenable to introduction of multiple amino acid modifications which can be expected to confer their separate advantages on

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the modified subtilisin, and because such an artisan would have been motivated to do so in view of the increasingly crowded art of subtilisin modification at the time the invention was made.

Claims 110-117 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bott et al. EP 0 357 157, made of record with Applicant's IDS filed 14 July 2003, in view of Branner et al., cited above, Brode et al. US 6,436,690, and Brode et al. US 6,455,295, both cited above.

Bott et al. '157 teach the preparation of variant subtilisins BPN' having improve its oxidative stability by making amino acid substitutions, such as substitution of an alanine or serine for any lysine, including the lysine at position 136 in subtilisin BPN', as well as detergent compositions comprising such variant subtilisins. See claims 3, 4, 9, and 10 and Figure 1. Teachings of Brode et al. '690 and Brode et al. '295, discussed above, of the amino acid substitutions of (i) asparagine for the amino acid present at the subtilisin BPN'-correspondent position 97, (ii) either alanine or asparagine for the amino acid present at the subtilisin BPN'-correspondent position 104, (iii) glutamate for the amino acid present at the subtilisin BPN'-correspondent position 206, (iv) serine for the amino acid present at the subtilisin BPN'-correspondent position 218, and that any of these substitutions may be advantageously combined with other substitutions in the subtilisins BPN' and Carlsberg, are taken as before as are those of Branner et al., of the preparation of variant, generic, subtilisins wherein amino acid substitutions, including K27R, H120D, and K235L, are advantageously made in "subtilisin BPN' [and] subtilisin Carlsberg".

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the amino acid sequence of the subtilisins BPN' and Carlsberg according to claims 110-112 and 114-116 herein, by preparing a variant subtilisin BPN', or a variant subtilisin Carlsberg, wherein a stabilizing substitution of alanine for lysine is made at the subtilisin BPN'-correspondent position 136 and to combine it with any of the K27R, H120D, and K235L substitutions of Branner et al. and to prepare detergent compositions of claims 113 and 117 herein comprising such multiply-modified subtilisins. This is because Bott et al. '157 teach the oxidative stability of a subtilisin is improved by replacing the lysine at such a position with valine, an uncharged amino acid, because Brode et al. teach that substitutions in subtilisins BPN' and Carlsberg at subtilisin BPN'-correspondent positions 97, 104, 206, and 218 are advantageously combined with further amino acid sequence modifications, because Branner et al. teach that the amino acid substitutions K27R, H120D, and K235L, are advantageously made in "subtilisin BPN' [and] subtilisin Carlsberg" and combined with further amino acid sequence modifications, and because such an artisan would have had a reasonable expectation of success in combining a K136A substitution of Bott et al. with one or more further amino acid sequence modifications made by Bott et al. and/or Branner et al. in the subtilisins BPN' and Carlsberg where Branner et

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al. teach that acid sequences of different subtilisin amino are amenable to multiple amino acid modifications which be expected to confer their separate advantages on the modified subtilisin, and because such an artisan would have been motivated to combine these substitutions in view of the increasingly crowded art of subtilisin modification at the time the invention was made.

#### *Conclusion*


Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/Nashed/

Nashaat T. Nashed, Ph.D.

Primary Examiner, Art Unit 1656

  
William W. Moore  
21 January 2008